Bar Flies

What our insect relatives can teach us about alcohol tolerance.

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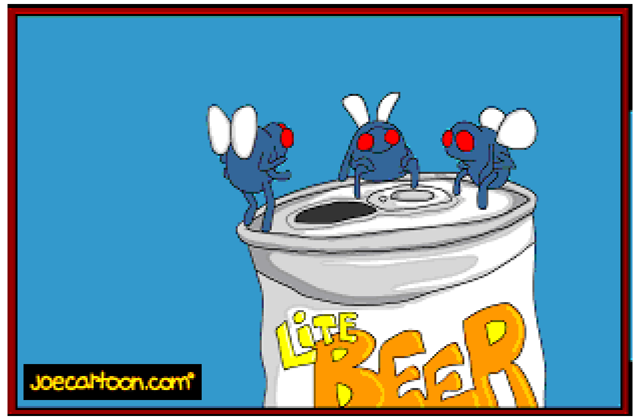

The life of a laboratory animal is not generally an enviable one. However, Ulrike Heberlein and her colleagues at the University of San Francisco study the effects of alcohol on fruitflies and so for these little insects it must be pretty pleasant work - as long as they can handle the hangovers! The problem for one particular strain, however, is that they can't. Unlike normal flies, the newly identified mutant strain, aptly named hangover, is unable to develop normal tolerance to alcohol. It is commonly known in humans that if you stop getting hangovers after heavy drinking, it's a bad sign. Indeed, repeated alcohol consumption leads to tolerance that can, in extreme cases, lead to dependence and even addiction. Since little is known about alcohol tolerance in humans, Heberlein's team were interested in studying fruitflies for their potential use as a model organism.

Staggering... The group randomly (but traceably) mutated fruitflies and then looked for mutants with aberrant alcohol tolerance. Using a device called an inebriometer (no joke!), they measured the flies' geotactic (orientation) and postural behaviours in response to ethanol vapours. Upon initial exposure, normal flies and hangover mutants showed signs of inebriation after 20mins. For normal flies this then increased to 28mins on subsequent exposure indicating that more alcohol is needed to elicit the same effect. For *hangover* flies, however, inebriation took only 22-23mins upon their second exposure indicating they had not developed normal tolerance. By searching the *hangover* fly's genome the team were able to trace the mutation to a gene coding for a previously unknown protein. To confirm that this gene was indeed responsible for reduced alcohol tolerance, they then corrected the mutation and showed that normal tolerance was restored.

Hung-over... In *hangover* flies alcohol tolerance is not completely ablated - it takes them a little longer to become inebriated the second time - and this indicates that another biochemical pathway might be involved. The Heberlein group have since found another mutant fly strain, deficient for the neuronal factor octopamine, which also shows reduced tolerance to alcohol. Now, by specifically mutating both the hangover and octopamine genes in the same fly, they have shown that alcohol tolerance is almost completely abolished. Interestingly, while octopamine seems to be specifically involved in alcohol tolerance, the protein coded by the *hangover* gene appears to participate in the cell's general stress response pathway - In *hangover* flies tolerance to other environmental stresses, including heat and oxidative stress (cell damage caused by free-radical formation) was also reduced.

A fly walks into a pub with a lump of tarmac under his arm and says to the barman "Pint of lager please...and one for the road"

In mammals there is growing evidence that stress, including stress at the cellular level, contributes to drug- and addiction-related behaviours. Heberlein's research therefore suggests that these pathways are also present in insects. Thus, while *hangover* mutant flies might not be able to hold their liquor, they might well hold the key to understanding drug and alcohol addiction in humans.

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